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PTENtiating autoimmunity through T_{reg} cell deregulation

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Summary

Regulatory T (T_{reg}) cells require PTEN to block PI3K signaling while maintaining Foxp3 expression. In the absence of PTEN, T_{reg} cells lose Foxp3 expression and their suppressive function, leading to a systemic increase in interferon- γ secretion, with consequent expansion of pathogenic T helper 1 and follicular B helper T cells and systemic autoimmunity.

Regulatory T (T_{reg}) cells dampen and promote resolution of the effector immune response, reducing both immunopathology and autoimmunity via secretion of the anti-inflammatory cytokine interleukin-10 (IL-10) and competition with effector T cells for interleukin-2 (IL-2) ¹. In this issue of *Nature Immunology*, Huynh, *et al.* and Shrestha, *et al.* demonstrate that the phosphatase PTEN protein maintains suppressive function of T_{reg} cells in homeostatic conditions through preserved expression of the high affinity IL-2 receptor (IL-2R α , also known as CD25) and their canonical transcription factor, forkhead box P3 (Foxp3) (Huynh, *et al.*, 2014; Shrestha, *et al.* 2014).

IL-2 is a known inducer of T_{reg} cell differentiation and maintenance, signaling through Signal Transducer and Activator of Transcription 5 (STAT5) to maintain Foxp3 expression ². IL-2 signaling is also mediated by phosphoinositide 3-kinase (PI3K) and activation of the metabolic checkpoint kinase mTOR in effector T cells, such as T helper 1 (T_H1) and T_H17 cells ³; however, differentiation of T_{reg} cells is not reliant upon signaling via this IL-2-dependent pathway (Fig. 1a). T_{reg} cells also do not upregulate glycolytic metabolism, instead preferentially utilizing fatty acids to promote their regulatory functions ⁴. PTEN is a potent negative regulator of PI3K signaling, utilizing its phosphatase activity to oppose PI3K-mediated conversion of the membrane-associated signaling molecule phosphatidylinositol-4,5-bisphosphate (PIP2) to PIP3 ³. In line with its role in immunoregulation, deletion of PTEN in CD4⁺ T cells leads to thymus-derived lymphoma and autoimmunity, although the T cell subset-intrinsic role for PTEN in regulating autoimmunity is unclear ⁵. PTEN is highly expressed in T_{reg} cells, and has been previously found to suppress T_{reg} cell expansion ⁶. Huynh, *et al.* and Shrestha, *et al.* now demonstrate that PTEN in T_{reg} cells is critical for control of autoimmunity, finding it essential for the maintenance of CD25 and Foxp3 expression (Fig. 1b). As a consequence, T_{reg} cell-intrinsic

expression of PTEN is necessary for the suppression of autoimmune responses mediated by T_H1 and follicular B helper T (T_{FH}) cells, drivers of B cell maturation, via attenuation of interferon- γ (IFN- γ) production.

Both studies take a genetic deletion approach, generating T

In line with changes in their suppressor function, qualitative differences in T_{reg} cell metabolism in the absence of PTEN were found by both sets of authors. Unlike effector cells, T_{reg} cells have a reduced reliance on glucose and anabolic metabolism for their development and maintenance, instead utilizing fatty acids to promote their suppressor capability⁴. PI3K induces anabolic metabolism through mTOR activation, consistent with the higher PTEN activity in T_{reg} cells compared to their effector counterparts³. PTEN deletion in the former led to upregulated glycolytic metabolism, further promoting the effector cell phenotype of these cells. As the effector counterparts require glucose for function, it would be interesting to know if the PTEN-deficient ex-T_{reg} cells required glucose for their autoimmune potential, and whether blockade of glucose uptake could rescue the T_{reg} cell phenotype and suppressive functions.

As further evidence of the reduced suppressive capacity of PTEN-deficient T_{reg} cells, mice bearing these mutant cells developed an autoimmune syndrome resembling systemic lupus erythematosus (SLE, lupus), with production of antinuclear autoantibodies (ANAs) leading to immune-complex glomerulonephritis. Pathogenic autoantibody production in murine and human lupus is mediated by exuberant activation of T_{FH} cells followed by aberrant germinal center (GC) B-cell responses, in line with the findings of Huynh, *et al.* and Shrestha, *et al.* Indeed, GCs are regulated by a specific T_{reg}-cell subset (follicular regulatory T cells, or T_{FR} cells), and the autoimmune phenotypes seen in the absence of T_{reg} PTEN are in line with reduced T_{FR}-mediated suppression. Additionally, Shrestha, *et al.* showed that IFN- γ is increased in all effector cells in animals with PTEN-deficient T_{reg} cells, reminiscent of several lupus-prone mouse strains, including the *Roquin^{san/san}* mouse, in which this cytokine is required for aberrant T_{FH} cell and GC B cell expansion and autoantibody production⁸. Accordingly, deletion of IFN- γ in the *Pten^{fl/fl}Foxp3-Cre* mice by Shrestha, *et al.* rescued the aberrant increase in T_{FH} and GC B cells and production of pathogen-specific antibodies. In addition to ex-T_{reg} cells, CD4⁺ and CD8⁺ T effector cells have an increase in IFN- γ secretion in the absence of PTEN in T_{reg} cells. While its increased secretion by CD4⁺ T cells is likely an autoimmune driver, it would be important to know the contribution of IFN- γ secretion to disease by all three lineages – T_{reg}, T_{FH} and effector T cells – as this has implications for understanding and treating autoimmunity resulting from defective suppression by T_{reg} cells.

The novel insights from the work of Huynh, *et al.* and Shrestha, *et al.* raise additional questions. Is T_H1-mediated autoimmunity mTORc2 regulated? The finding that mTORc2 upregulation enables T_{reg} cells to adopt a T_H1 phenotype was surprising, given that mTORc1 has been found to promote T_H1 differentiation, with mTORc2 promoting that of T_H2 cells³. Thus, it is possible that mTORc2 is a critical regulator of T_H1-cell function, particularly via IFN- γ upregulation. It was also interesting that T_{reg} cell dysfunction led to selective expansion of T_H1 and T_{FH} cells through the induction of IFN- γ , and not to the

proliferation of other T cell subsets. How is IFN- γ pathogenically induced in these contexts? Could reduced T_{reg} cell suppression be the key to loss of immune tolerance? Indeed, these authors find that deletion of PTEN from T_{reg} cells can recapitulate many of the autoimmune phenotypes of mice globally deficient in PTEN. Future studies in human autoimmune syndromes, particularly those driven by IFN- γ signaling, are required to determine whether T_{reg} cell deregulation is a principal mediator of disease pathogenesis. How PI3K prevents T_{reg} cell function is also unknown; however, Shrestha, *et al.* found that Blimp-1 is upregulated in the absence of PTEN, suggesting that IL-2-signaling, known to induce this transcriptional regulator, does so via induction of PI3K signaling. The authors speculate that PTEN reduces PI3K-mediated Blimp-1 upregulation, allowing for prolonged IL-2 signaling within these cells. However, further experiments are required to parse the requirements of PI3K and STAT5 in inducing Blimp-1, as STAT5 has also been found to be an important regulator of its expression, at least in part through maintaining cell surface expression of CD25⁹.

The studies conducted by Huynh *et al.* and Shrestha *et al.* support the rationale for IFN- γ blockade in humans with SLE. Furthermore, their studies emphasize that deregulation of T_{reg} cells might be a primary driver of systemic autoimmunity, and conversely that their modulation or adoptive transfer might be beneficial. For example, rapamycin, known to promote T_{reg} cell proliferation at the expense of that of effector cells, is therapeutically beneficial in SLE¹⁰, while transfers of T_{reg} cells is efficacious in murine lupus models¹¹. Similar approaches are in clinical trials of type I diabetes mellitus (<http://clinicaltrials.gov/ct2/show/NCT01210664?term=type+1+diabetes+and+tregcells&rank=1/>). These clinical approaches highlight the broad implications of the findings of Huynh *et al.* and Shrestha *et al.* that PTEN is critical for T_{reg} cell suppression of potentially pathogenic T cells in non-infectious conditions.

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1. Please use smaller font size, compared to the cell on the left, for:

STAT5
Cd25 and CD25
both Foxp3s
Immune suppression

2. Please add a cross out mark (an "X") to PTEN

3. Please change solid lines, below PI3K leading to mTORc2, and below mTORc2 leading to Blimp-1, to dotted lines

Figure 1.

Regulatory T (T_{reg}) cells modulate their IL-2 signaling to maintain their suppressive function through PTEN. (a) T_{reg} cells express high amounts of PTEN, which abrogates PI3K signaling downstream of IL-2. (b) PTEN-deficient T_{reg} cells lose their suppressive function, due to reduced maintenance of Foxp3. Conversely, these cells have enhanced mTORc2 signaling, eliciting T_H1 cell effector functions in a cell intrinsic manner. Red indicates suppressive pathways. Solid lines have been experimentally tested, whereas dashed lines are postulated signaling pathways, with mTORc2 presumably operating downstream of PI3K.